Statistical Analysis Plan

Full Title of Study	A Phase 2 Study of Gemcitabine plus BPM31510 [redacted] Nanosuspension Injection Administered Intravenously with Gemcitabine as 2nd/3rd line therapy in Advanced Pancreatic Cancer Patients
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1.0 List of Abbreviations

Abbreviation	Full Term
AE	adverse event
ALT (SGPT)	alanine aminotransferase
ALP	alkaline phosphatase
AST (SGOT)	aspartate aminotransferase
ATAS	adequately treated analysis set
BPM	Berg Molecule
BUN	blood urea nitrogen
CA 19-9	cancer antigen 19-9
CA 125	cancer antigen 125
CEA	carcinoembryonic antigen
CR	complete response
CRAB	Cancer Research and Biostatistics
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
FDA	Food and Drug Administration
FACT-Hep	Functional Assessment of Cancer Therapy – HEP
GGT	gamma glutamyl transferase
INR	International Normalized Ratio
LLN	Lower Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities
NE	Not evaluated
ORR	overall response rate
OS	overall survival
PD	progressive disease
PET	Positron Emission Tomography
PFS	progression free survival
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
RECIST	Response Evaluation Criteria in Solid Tumors (v1.1)
SAE	serious adverse event
SD	stable disease
TTP	time to progression
ULN	Upper Limit of Normal
WBC	white blood cell

2.0 Introduction

This Statistical Analysis Plan (SAP) describes the analyses for the study entitled: "A Phase 2 Study of Gemcitabine plus BPM31510 [redacted] Nanosuspension Injection Administered Intravenously with Gemcitabine as 2nd/3rd line therapy in Advanced Pancreatic Cancer Patients."

The purpose of this document is to ensure that adequate and appropriate statistical approaches and data handling conventions for key analyses are performed to determine study outcomes. This plan will focus on the analysis of the primary endpoint, which is the assessment of overall response rate in patients treated with BPM31510 or with the combination of BPM31510 and Gemcitabine. Secondary endpoints will also be described, including best response, disease control rate, overall survival, progression-free survival, time to progression, duration of response, toxicity profiles, quality of life (QOL), and change in CA 19-9 levels. The analyses of the primary and secondary endpoints will be described, the populations for analysis defined, and all the rules specified for "data handling" relevant to undertaking the key analyses will be discussed.

3.0 Study Objectives and Endpoints

3.1 Overview of Study

This is a Phase 2 multicenter, open-label, non-randomized study to examine the safety and effectiveness of the combination of BPM31510 plus Gemcitabine in advanced pancreatic cancer patients as 2nd or 3rd line therapy. The primary safety endpoint is to determine the safety of BPM31510 as a combination therapy in this patient population. The primary efficacy endpoint is overall response rate. This study will occur in two parts. Part 1 of the study will enroll ten (10) evaluable patients. If at least one of ten patients treated experiences a complete response (CR) or partial response (PR), based on RECIST 1.1 criteria after 2 cycles of treatment, then Part 2 of the study will enroll an additional fifteen (15) for a total of 25 patients. In the absence of at least one CR or PR, if at least 3 patients experience stable disease the Sponsor can choose to enroll an additional 15 patients into the expansion stage.

3.2 Study Schedule and Assessments

Study drug will be administered over a maximum of twelve cycles. [redacted]

[redacted] Assessments of the antitumor activity of BPM31510 will be performed following the end of Cycle 2 and every two cycles thereafter using standard techniques such as computerized tomography (CT) or magnetic resonance imaging (MRI) for patients with measurable disease. An 18-fluorodeoxyglucose (18-FDG) PET scan will be performed within 14 days prior to starting treatment, at the end of Week 2 and then again at the end of Cycle 2, and then after every additional two cycles of completed treatment. The complete schedule of events can be found in Appendix D of the study protocol.

4.0 Study Objectives and Endpoints

4.1 Study Objectives: Primary

- To evaluate the Overall Response Rate in patients treated with the combination of BPM31510 with Gemcitabine.

4.2 Study Objectives: Secondary

- To evaluate Overall Survival
- To evaluate Progression-Free Survival [redacted]
- To evaluate Time to Progression (TTP);
- To evaluate Tumor Response using Adaptive Molecular Responses (epi-genomic analysis (SNP or X-omen technology))
- To determine the toxicity profile of BPM31510 in combination with gemcitabine when administered as a 144-hour (two 72-hr) intravenous (IV) infusion in patients with advanced pancreatic cancer.
- To evaluate change in CA 19-9 levels between baseline and subsequent treatment cycles
- To evaluate changes in patient reported Quality of Life using the validated FACT-HEP patient-reported outcomes instrument specific for patients with hepatobiliary and pancreatic cancers at the end of Cycle 2 and at End of Study or Early Termination

4.3 Study Objectives: Exploratory

- To evaluate the effects of BPM31510 on shifting tumors to aerobic respiration by PET imaging.
- Plasma and urine samples will be assayed for levels of markers of BPM31510 activity using (but not limited to): genomic (e.g. microarray, SAGE, northern blotting, gene expression), proteomic (e.g., LC/MS based analysis, 2DE-MS,

MALDI TOF, antibody array, ELISA, immunohistochemistry, tissue microarray, flow cytometry, western blotting),metabolomics (e.g., global analysis of metabolites in biological samples; identification of specific markers of energy metabolism e.g., pyruvate, lactate), lipidomic (e.g., global analysis of lipid classes; identification of specific lipids e.g., derivatives of palmitate, linoleic acid, arachidonic acid).

The objective of this integrative approach is to stratify patient populations based on phenotypic or molecular profiles for therapeutic benefit. This includes assessing the patient's biofluid as well as the tumor for markers of positive, stable or negative outcome allowing for guidance of selection of participants in future cohorts.

4.4 Study Endpoints: Primary Endpoint

Overall Response Rate

4.5 Study Endpoints: Secondary Endpoint

- Disease control rate (CR+PR+SD)
- Duration of response
- Overall survival
- Progression-free survival
- Time to progression
- FACT-Hep overall score and subscales
- CA 19-9 level change

Safety: Laboratory results, adverse events, vital signs, concomitant medications, concomitant procedures and ECG.

4.6 Study Endpoints: Exploratory Endpoint

Tumor response as measured by 18-FDG PET

4.7 Response

Per RECIST criteria as described in Appendix E of the protocol, determination of response is based on evaluation of Target and non-Target lesions for patients with measurable disease at baseline.

4.7.1 Evaluation of Target Lesions

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Stable Disease (SD)	Neither enough shrinkage to qualify for PR nor enough increase to qualify for PD, taking as reference the smallest sum diameters while on study.
Progressive Disease	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

4.7.2 Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. When the patient also has measurable disease, to achieve "unequivocal progression" based on the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

4.7.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the

smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Per RECIST, confirmation of response (by repeat scans after 4 weeks or as specified in the protocol) is required for this study in which response rate is the primary endpoint.

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
CR	CR	NO	CR
CR	NON-CR/NON-PD	NO	PR
CR	NE	NO	PR
PR	NON-PD OR NE	NO	PR
SD	NON-PD OR NE	NO	SD
NOT ALL EVALUATED	NON-PD	NO	NE
PD	ANY	YES OR NO	PD
ANY	PD	YES OR NO	PD
ANY	ANY	YES	PD

5.0 Populations for Analysis

5.1 Safety Population

The Safety Population is defined as all patients who are enrolled to treatment and receive at least one dose of BPM31510.

5.2 Intent to Treat (ITT)

The Intent to Treat (ITT) population will consist of all patients who are enrolled to treatment and may or may not meet inclusion/exclusion criteria. Those subjects not having met inclusion/exclusion criteria received a waiver by the study medical monitor.

5.3 Adequately Treated Analysis Set (ATAS)

The Adequately Treated Analysis Set (ATAS) is defined as all patients who meet inclusion/exclusion criteria, complete at least the first two cycles of therapy with a total of at least 18 days of drug infusion during Cycle 1 and at least 12 days of drug infusion during Cycle 2, and have an initial evaluation of response following the end of the second cycle such that an overall response is considered evaluable based on RECIST 1.1 criteria.

6.0 Statistical Methods and Determination of Sample Size

6.1 Determination of Sample Size

For each treatment arm, Part 1 of the study will enroll until at least ten (10) patients are accrued to the adequately treated analysis set (ATAS). If at least one of the first ten patients experiences a Complete Response (CR) or Partial Response (PR) based on RECIST 1.1 criteria after 2 cycles of treatment, then Part 2 of the study will enroll an additional fifteen (15) patients in that treatment arm, for a total of 25 patients in that arm. In the absence of at least one CR or PR, if at least 3 patients experience stable disease in a given treatment arm, the Sponsor can choose to enroll the additional 15 patients into that arm in the expansion stage.

For each treatment arm, this two-stage design enrolls 10 patients in the first phase and 15 patients in the second phase, with continuation to the second phase of enrollment if at least one response (CR or PR) is observed in the first 10 patients. [redacted]

6.2 Statistical Considerations

Statistical analyses will be descriptive. All analyses will be presented by treatment arm (BPM31510 or BPM31510 plus Gemcitabine) unless otherwise indicated. If there are subjects enrolled on BPM31510 monotherapy, then the data will be analyzed in the tables descriptively (ITT Population) but not inferentially. Total frequencies and percentages will be presented for categorical variables. Mean, median, standard deviation, and range will be presented for continuous variables, both overall and by treatment arm unless otherwise specified. All analyses will be based on the study populations as defined in Section 4.0 unless otherwise indicated. Exact 95% confidence intervals will be computed for selected proportions using the Clopper-Pearson method.

6.2.1 Demographic and Baseline Data

Demographics

Demographic characteristics will be summarized for all analysis populations as defined in section 4.0 (Safety population, ITT population, and ATAS). The total counts and percentages of patients will be presented for the categorical variables. The mean, median, standard deviation, and range will be presented for continuous variables. Demographics to be summarized include age, sex, race, and ethnicity. Age in years (defined as the date of signed informed consent minus the date of birth divided by 365.25 days truncated to the lowest integer) will be summarized as both a continuous variable and categorical variable, with grouping done as < 60 years, 60-69 years, and ≥ 70 years.

Baseline Patient Characteristics

The Pre-Study visit will occur within 14 days prior to randomization and baseline values are collected within the time frame given in the protocol Schedule of Events. Baseline values for vital signs and physical examination findings are defined as the last reported values prior to first dose of study drug.

Baseline characteristics will be summarized for all analysis populations as defined in section 4.0 (Safety population, ITT population, and ATAS). Baseline characteristics to be summarized include height, weight, ECOG performance status, and the number of reported prior pancreatic cancer therapies.

Pregnancy test: Positive results will be listed only, along with method (urine or plasma)

Physical Examination at Baseline: Frequency table of patients with at least one abnormal finding.

The total counts and percentages of patients will be presented for the categorical variables. The mean, median, standard deviation, and range will be presented for continuous variables.

6.2.2 Patient Disposition

The numbers and percentages of patients who were enrolled and who are included in the safety, ITT, and adequately treated analysis sets will be summarized. The number and percentages of patients who discontinued from the study and the reason for discontinuation will also be presented.

The treatment group, date of enrollment, date of first dose, date of last dose, date of discontinuation, and reason for discontinuation will be listed for each patient.

6.2.3 Medical History

Medical history will be summarized by treatment group using data from the "Baseline Abnormalities /Medical History" eCRF page. Medical history is coded with MedDRA version 19.0. Medical history will be displayed in terms of frequency tables: ordered by primary system organ class (SOC) and preferred term (PT) in decreasing frequency order:

Medical history will be listed by treatment group and patient number.

In case of partial or missing end date, medical history will be assumed to be ongoing

6.2.4 Concomitant and Prior Medications

Concomitant medications are defined as all non-study medications, including any herbal preparations, indicated as having been taken on or after the patient's date of informed consent and prior to the patient's date of discontinuation from the study. Medications with partial onset dates that indicate usage starting on or after the date of informed consent, including such medications with completely missing stop dates, will be classified as concomitant. Prior medications are defined as all medications classified as concomitant and indicated as prior therapies in the CRF.

Prior medications preceding study drug administration will be presented and will be summarized for analysis in the ITT population by assigned treatment. Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary as of September 2017. Levels of summarization will include global, WHO Anatomic Therapeutic Chemical (ATC) Level II drug class, and WHO generic term. At each level of summarization, a patient will be counted only once for each concurrent medication he/she has within that level. The percentage of patients having had at least one medication at each level will be calculated.

6.2.5 Efficacy Analyses

All efficacy analyses will be performed on the adequately treated analysis set (ATAS) unless otherwise noted, separately for each treatment arm.

6.2.5.1 Primary Endpoint - Tumor Response

Objective responses will be evaluated using RECIST 1.1 as described in Section 3.6 above. To compute a response rate, the number of patients who achieved a

specific level of response will be divided by the number of patients in the adequately treated analysis set. Assessments based on response will include objective response rate based on best response (ORR: CR+PR) and response frequencies including disease control rate (DCR: CR+PR+SD) at each assessment. When a CR or PR is documented, a confirmatory scan will be obtained per RECIST guidelines.

6.2.5.2 Time to Event Endpoints

The distribution of time-to-event endpoints will be estimated using the method of Kaplan-Meier (Kaplan and Meier, 1957). The Kaplan-Meier method will be used to obtain estimates at every six-month interval after enrollment for which at least one patient is still alive for the probabilities of patients surviving. Kaplan-Meier curves will be presented, with the median presented along with the associated 95% confidence interval using the Brookmeyer-Crowley method

Progression Free Survival

Progression-free survival (PFS) is defined as the number of days from the first dose of study drug to the first documentation of progression or death due to any cause. Patients who remain alive without progression will be censored for PFS at the date of their last tumor assessment.

Time to Progression

Time to Progression (TTP) is defined as the number of days from the first dose of study drug to the first documentation of progression. Patients without progression will be censored at the date of their last tumor assessment.

Overall Survival

Overall survival is defined as the number of days from the first dose of study drug to the date of death due to any cause. Patients alive at the time of analysis will be censored at the date of last contact.

Duration of Response

Duration of response is defined as the number of days from the first observation of response to the first observation of progression, or death. For patients who have not progressed, duration of response is censored at the time of last follow-up.

6.2.6 Safety Analyses

All patients who have received at least one dose of study medication (BPM31510) will be considered evaluable for safety.

Safety assessments will be based on adverse events (AEs) and serious adverse events (SAEs), measurement of protocol-specified hematology, measures of coagulation (PT,

PTT, and INR), clinical chemistry, and urinalysis variables, measurement of protocol-specified vital signs, and other protocol-specified tests that are deemed critical to the safety evaluation of the trial drug. Selected laboratory measurements will be graded using CTCAE criteria. Adverse Events will be coded using MedDRA 19.0 (or the most current version specified by the study safety management plan). Toxicity grading will be defined using CTCAE v4.02.

Safety observations and measurements including study drug exposure, adverse events, laboratory data, ECG findings, vital signs, and ECOG performance status will be summarized using descriptive statistics. Adverse events and serious adverse events will be tabulated by Preferred Term and maximum grade for each type of toxicity within a patient. Laboratory test results will be summarized using values observed at each visit and shift from baseline values.

Selected event types (such as death data and SAE) will be reflected in listings.

6.2.6.1 Adverse Events

All AEs and SAEs will be collected and reported in the patient's eCRF throughout study duration (i.e. from the first trial related activity after the subject signs the informed consent and until 30 days after last administration of BPM31510). All AEs along with the coded terms will be listed.

Adverse Event (AE): Any untoward medical occurrence or deterioration of a pre-existing medical condition in a patient or clinical investigation subject following or during exposure to an investigational product.

Serious Adverse Events (SAE): An adverse event or suspected adverse reaction is considered "serious", if it results in any of the outcomes: Death, a life-threatening adverse drug experience, requires at least a 24-hour inpatient hospitalization or prolongation of existing hospitalization., a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, a congenital anomaly/birth defect.

The following general rules apply to adverse events

- TEAEs are defined as those AEs that started on or after the first dose of study medication or that worsened after the first dose of study medication and with an onset date occurring during the treatment period.
- The treatment period is defined from the first dosing day of study treatment (minimum of the first dosing day for BPM31510, gemcitabine) until the last dose of study treatment. (maximum of the last dosing day BPM31510, gemcitabine) plus 30 days. If an AE is reported for a given patient more than once during treatment, the worst severity and the worst relationship to study treatment will be tabulated.
- In table summaries, patients will be counted only once at the PT level if multiple incidences of the same event occur within a SOC. Patients will be counted only once at the SOC level if multiple events occur within that SOC. For example, a patient who

experiences an event of anemia and an event of neutropenia will be counted twice at the PT level (anemia, neutropenia) and once at the SOC level (vascular disorders)

- Investigator-assessed causality and relationship to study drugs will also be presented.
- In case a subject had AEs with missing and non-missing grades, the maximum of the nonmissing grades will be displayed.

The start dates for AEs are important for the following:

1- Derivation of TEAE algorithm. A TEAE is an event that first occurred or worsened in severity after baseline.

2- Designation of unique AE occurrences.

3- Completely missing or partially missing AE onset dates will be imputed after due diligence to obtain accurate AE information has failed. The imputation will consider the start and stop dates relative to the each other, and relative to the date of consent and date of first dose.

AEs with start dates that are completely or partially missing will be analyzed as follows:

- If the event start date is completely missing, then the event is assumed to be treatment-emergent.
- If the start date has the month and year but day is missing, the event will be considered treatment-emergent if the month and year of the event start date are equal to, or greater than, the month and year of the date of first dose of study drug.
- If the start date has the year, but day and month are missing, the event will be considered treatment-emergent if the year of the event start date is to the same as, or later than, the year of the date of the first dose of study drug.

Only TEAEs will be summarized. The incidence of TEAEs will be presented by the number and percent of patients who experienced the TEAE by SOC and PT.

All deaths and deaths occurring during the study (i.e. deaths after start of treatment and within 30 days after last dose of study treatment) as recorded in the "End of Study" eCRF section will be tabulated by treatment group. In addition, dates will be provided in individual patient data listings together with related AE information (PT, verbatim term from eCRF, start date of AE, end date of AE, related to BPM31510 (Yes/No), and action taken).

In an overall AE summary table, the Incidence of treatment-related TEAEs will be summarized by SOC and PT (in alphabetic order) for patients experiencing at least one:

- TEAE
- Grade 3 or 4 TEAE
- Grade 3 or 4 study-drug related TEAE
- Study drug-related TEAE
- TEAEs by maximum intensity based on CTCAE grade
- SAE
- Study drug-related SAE

- TEAE resulting in study drug discontinuation
- TEAE with an outcome of death
- TEAE of special Interest- Increased PT/PTT/INR, Bleeding events and ≥ Grade 3 increased LFTs considered related to BPM31510.

Results will be presented by treatment arm and overall. Adverse events will also be summarized using subject incidence rates by treatment group, SOC, and MedDRA preferred term. Therefore, in any tabulation, a subject contributes only once to the count for a given adverse event (preferred term). Further summaries by preferred term will include summaries for treatment related TEAEs, TEAEs with CTC Grade 3 or 4, treatment Related TEAEs with CTC Grade 3 or 4, serious TEAEs, treatment Related SAEs, TEAEs Occurring in at least 5% of patients in either treatment group, and deaths.

SAEs will be followed until the event resolves.

All AEs reported in the eCRF will be listed with the SOC, PT and Investigator's verbatim term.

Assessing Severity of Adverse Events

The NCI CTCAE v4.02 will be used to assign the following severity scale to AEs.

- Grade 1 = Mild
- Grade 2 = Moderate
- Grade 3 = Severe
- Grade 4 = Life Threatening
- Grade 5 = Death

AEs that are not defined in the NCI CTCAE should be evaluated for severity according to the following scale:

- Grade 1 = Mild
- Grade 2 = Moderate
- Grade 3 = Severe

In addition, all AEs reported using the NCI CTCAE classification and graded as 4 or 5 are to be considered serious.

The criteria for assessing severity are different than those used for seriousness.

Classification of Causality

Causality is a determination of whether there is a reasonable possibility that the study drug may have caused or contributed to an adverse event.

Not Related: A causal relationship between the study treatment and the AE is not a reasonable possibility.

Related: A causal relationship between the study treatment and the AE is a reasonable possibility. Further the degree of certainty of relatedness is classified as **Unlikely**, **Possible, Probable, Definite, Unknown.**

6.2.6.2. Clinical Laboratory Data

Local laboratories are being used for this clinical study for all the laboratory tests. For each individual laboratory used, laboratory reference ranges and units are collected. Reference ranges will be entered into the local laboratory normal range. Vitamin K and

advanced coagulation testing (for Grade 2 increases in INR) may be performed through local laboratory or through the central laboratory.

The laboratory collection CRFs (hematology and serum chemistry) include fields for additional, nonprotocol-required clinically significant laboratory tests, including laboratory test name, result, units, normal range low, and normal range high.

NCI CTCAE version v4.02 will be used for grading applicable laboratory tests.

Standard biological assessments will be performed at the local laboratory of the Investigator ‘s site at selection, before any BPM31510 administration and at the end of each course of chemotherapy as follows:

- **Hematology**: complete blood count (CBC) with differential, platelets;
- **Coagulation**: partial thromboplastin time (PTT), prothrombin time (PT), INR (Screening only: Vitamin K)
- **Serum chemistry**: Albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen (BUN), calcium, carbon dioxide, chloride, creatinine, gamma-glut amyl transferase (GGT), glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total bilirubin, total protein, serum magnesium, cholesterol, triglycerides
- **Urinalysis:** Appearance, color, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, and occult blood (microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive)
- **Laboratory work-up for any ≥ grade 2 INR:** LFTs, levels of Vitamin-K dependent coagulation factors (II, VII, IX, X), Protein C, and Protein S. If ≥ grade 2 INR is not corrected following administration of Vitamin K, cryoprecipitate or fresh frozen plasma, additional tests such as mixing studies, fibrinogen level, D-dimer and fibrin split products is performed.

For laboratory parameters (i.e., hematology, coagulation, serum chemistry and urinalysis), shift analyses will be performed on laboratory abnormalities of the highest NCI CTCAE grade or the worst severity if there is no NCI CTCAE grade. Shifts from baseline will be classified as improved from baseline, no change from baseline, or worsened from baseline. These summaries will be presented by treatment group and overall.

All laboratory data will be provided in data listings. A subset listing will be presented for all clinically significant abnormal laboratory values. This listing will present all lab values for any parameter with at least one clinically significant abnormal value so that a time course for that lab parameter can be presented.

6.2.6.3 Vital Signs and Performance Status

Vital signs parameters, measured in supine position, will include body temperature (°C), height (cm, measured only at baseline), weight (kg), heart rate (beats/min), systolic and diastolic blood pressures (mmHg) and will be evaluated by treatment group and overall. For Vital signs, shift tables from baseline to post-baseline values will be presented by treatment groups and overall. And among the three assessments (pre-dose, post infusion

and before discharge), for post-baseline results consider before discharge assessment. If before discharge is absent then consider post-infusion assessment.
For ECOG Performance Status, shift tables from baseline to worst post-baseline values (normal, abnormal not clinically significant, abnormal clinically significant, missing) will be presented by treatment group and overall.
By-subject listings of all vital sign and ECOG measurements will also be presented in data listings.

6.2.7 Evaluation of Exploratory Parameters

CA 19-9

Change in CA 19-9 levels will be summarized by shift table to compare levels between baseline and subsequent cycles in the adequately treated analysis set.

Pharmacodynamics and Adaptive Molecular Responses

Blood samples will be collected for PD during BPM31510 treatment. PET scans performed will be evaluated for the Warburg effect by BPM31510 in the tumors. Up to five (5) core biopsy tissue samples will be collected for pathology and exploratory studies in patients who choose to participate. Core biopsies are prohibited with patients who have tumors that are highly vascular, located near major blood vessels or are proximal to vital organs.

Exploratory PD analyses will be performed on blood and urine samples and biopsy samples assayed for markers of BPM31510 activity using (but not limited to) genomic (e.g., microarray, SAGE, northern blotting, gene expression), proteomic (e.g., LC/MS based analysis, 2DEMS, MALDI TOF, antibody array, ELISA, immunohistochemistry, tissue microarray, flow cytometry, western blotting), metabolomics (e.g., global analysis of metabolites in biological samples; identification of specific markers of energy metabolism e.g., pyruvate, lactate), lipidomic (e.g., global analysis of lipid classes; identification of specific lipids e.g., derivatives of palmitate, linoleic acid, arachidonic acid).

The exploratory endpoints and subsequent analyses will be defined by molecular characteristics of patient populations that demonstrate predictive power in associating a profile of response, stable disease, or lack of efficacy to guide clinical decision making

Tumor Response by FDG-PET

Comparisons between baseline and follow-up PET imaging will be evaluated for response as determined by the local investigator and/or changes in SUV in a target lesion from baseline. This will likely be a binary endpoint, with the time point of primary

interest being 10 weeks after start of treatment (2 treatment cycles). The primary analysis of this exploratory endpoint will be carried out in the adequately treated analysis set.

6.2.8 Quality of Life Analyses

Quality of Life assessments will be based on the FACT-Hep instrument, which includes 18 items that assess specific symptoms for hepatobiliary and pancreatic cancers, all rated on a 5-point scale ranging from 0 (not at all) to 4 (very much). Change from baseline to 10 weeks, and from baseline to end of treatment, will be summarized and analyzed descriptively for the overall score as defined by the instrument, and for each of the following sub-scores:

PWB - Physical Well-Being subscale
SWB - Social/Family Well-Being subscale
EWB - Emotional Well-Being subscale
FWB - Functional Well-Being subscale
AC - Additional Concerns
FACT-Hep Total Score (i.e., PWB+SWB+EWB+FWB+AC)

6.2.9 Sensitivity Analyses

Sensitivity analyses will be performed for efficacy measures on the ITT population. Sensitivity analyses will be performed for safety on the adequately treated analysis set. Sensitivity analyses performed will include best response rate, disease control rate, overall survival, progression-free survival, time to progression, and summaries of adverse events.

6.2.10 Planned Interim Analyses

No formal interim analysis is planned except for the analysis of response in the first 10 enrolled patients in each treatment arm as described above in Section 5.1.

6.3 Drug Exposure

Cycle 1 of therapy is 6 weeks in duration for patients with BPM31510 administered twice weekly on Tuesdays and Fridays for 6 weeks. Patients will be treated with gemcitabine administered on Mondays, Days 21, 28 and 35 during the first treatment cycle. Response will be assessed after Cycle 2 (10 weeks) and patients who continue onto Cycles 3-12 will be assessed every 2 cycles (8 weeks). Cycles 2-12 are 4 weeks in duration with BPM31510 administered twice weekly on Tuesdays and Fridays for 4 weeks and gemcitabine administered on Mondays, Days 7, 14 and 21 of each treatment cycle.

For patients receiving an alternate dosing schedule, the gemcitabine chemotherapy treatment will be given after the completion of the sixth infusion (three weeks following initiation of BPM31510 treatment).

If the gemcitabine component of combination therapy is discontinued due to chemotherapy-related toxicity, patients may continue to receive BPM31510 as monotherapy at the investigator's discretion.

Analysis of all exposure to study drug will be based on the safety population. Overall exposure to study drug, the number of patients completing each cycle, and the dose intensity will be summarized using descriptive statistics.

The dose intensity (for a cycle and overall) will be computed as (total actual dose received)/ (total actual dose expected) x 100. In addition to dose intensity, other measures will be presented, as appropriate.

6.3.1. Treatment Duration

Patients who experience no unacceptable toxicity or disease progression while on BPM31510 for 2 cycles of therapy (10 weeks) may receive additional 28-day cycles of their current treatment for up to 1 year (12 cycles) or until any of the discontinuation criteria listed in Section 3.4 are met.

Patients who experience disease progression but are, in the opinion of the investigator, receiving clinical benefit may continue BPM31510 as a monotherapy or in combination with gemcitabine with approval from the Sponsor.

Treatment duration in weeks will be defined as: (last injection date – first injection date) / 7.

6.3.2. Compliance

For each therapy, overall compliance (%) will be defined as: number of injections received/number of injections planned

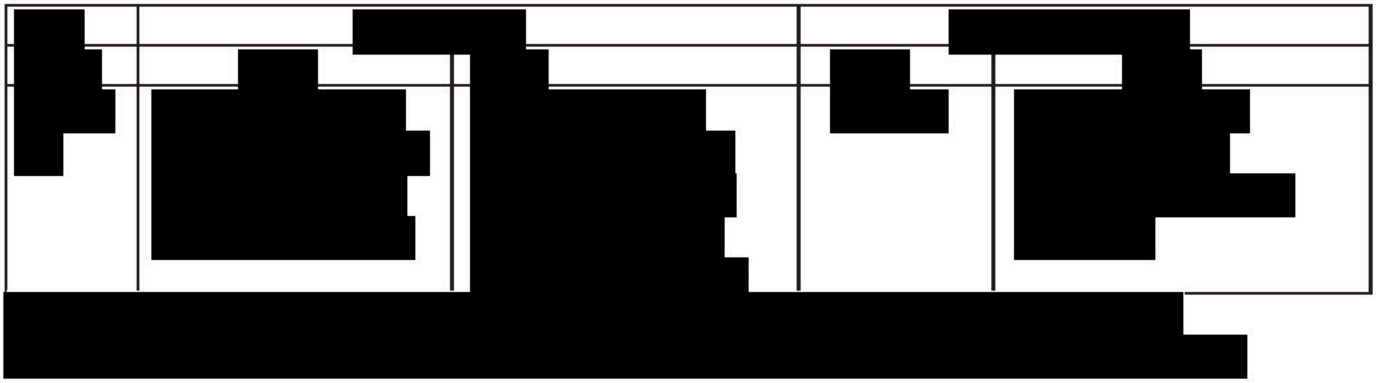
Based on the definitions above, the following summary tables will be provided for BPM31510 combination with gemcitabine as well as for each therapy separately (BPM31510/gemcitabine) unless otherwise noted:

- Study duration (weeks): summary statistics,
- Treatment duration (weeks): summary statistics,
- Total number of cycles with therapy Intake (i.e., number of infusions): summary statistics (overall by treatment group and broken down by each individual therapy)
- Compliance: summary statistics and frequency table for the categories <60%, 60% to <80%, 80% to 100%, >100%.

6.3.3. Dose Modification

Dose Modification for BPM31510 Doses

Dose modification based on type of toxicity (hematologic vs non-hematologic) and grade is provided to guide BPM31510 dosing decisions.



Dose Modification for Chemotherapy-Specific Toxicity

For toxicities that are likely to be due to gemcitabine, reduction of gemcitabine dose will be permitted. The dose reduction of gemcitabine will be step-wise, to the next lowest dose as in below table. Toxicities requiring dose reductions should be documented as adverse events.

Patients may continue to receive BPM31510 as monotherapy if the gemcitabine component of combination therapy is discontinued due to toxicity.

Gemcitabine: Gemcitabine dose levels are 600 mg/m2, 800 mg/m2, and 1000 mg/m2.

Toxicity	**ANC (x 10^6/L)**	**Platelet count (x 10^6/L)**	**Management**
Myelosuppression	$\geq$ 1000 and $\geq$ 75,000		OK to treat.
	500-999 or 50,000-75,000		Hold chemotherapy. Resume if ANC $\geq$ 1000 and PLT $\geq$ 75,000 at 1 dose level reduction to 800
	< 500 or < 50,000		Discontinue further gemcitabine.

6.3.4. Dosing Delays during Cycles 2-12

If the criteria for managing toxicity specified in Section 6.3.2 are not met, BPM31510 treatment may be delayed for a maximum of 2 weeks during Cycles 2-12. The patient may resume treatment if treatment is held for less than 2 weeks. No more than 2 weeks may be skipped within a cycle. If treatment cannot be given after a 2-week delay, the patient will be removed from the study and followed for 30 days from the date of the last dose.

6.3.5 Dose Interruptions

Due to Hemodynamic Instability

If there is hemodynamic instability at any time during the BPM31510 infusion (loading dose or ambulatory infusion), the infusion will be stopped.
The infusion is restarted at ½ the rate.

Due to Infusion Pump Malfunction Outside of the Clinic

The dosing interruption are captured as pump malfunction and delay on the dose eCRF. Data regarding the exact amount infused, the duration of any stoppage, and the volume remaining in the cassette at the time the infusion was discontinued are recorded in eCRF.

6.4 Data Handling Rules

- **Conversions from Days to Years, Months or Weeks**

  Years = # of days / 365.25
  Months = # of days / 30.4375 (i.e. 365.25/12)
  Weeks = # of days / 7

  Values based on the above computations will be rounded to tenths.

- **Computation of Duration**

  Duration for time variables based on two dates, e.g., Start Date and End Date, will be calculated as (End Date – Start Date + 1) (in days) unless otherwise specified.

- **Missing normal ranges for laboratory parameters**

  When either the lower limit of normal, the upper limit of normal or both are missing or are not machine readable, a standardized reference range will be used.

- **Non-Numeric Laboratory Results and Calculation of Normal Ranges**

  Laboratory values including symbols (“<” or “>”, for example) will not be used in summary analyses. These values will be reflected in listings of the data. When there

are potential conflicts between local lab normal ranges and ranges used in CTC grading, CTC normal ranges will be used.

- **Missing outcome data**

  For partial dates affecting calculations of clinical outcomes, missing month will be imputed with January and missing day will be imputed with 1. Non-ignorable missing quality of life data are a common problem in advanced stage disease trials. The primary analysis of QOL data will focus on the shorter-term time point of 10 weeks. For explorations of later time points, analytic techniques such as pattern mixture models will be used in the event of informative missing data for the FACT hep.

6.5 Changes from protocol-specified analysis

The definition of the adequately treated analysis set has been modified from the protocol. The protocol states that patients withdrawn from treatment for any reason prior to completion of 2 cycles will be replaced. The subset of patients to be replaced for the adequately treated analysis set has been augmented in this SAP to also include patients who fail to receive at least 18 days of BPM31510 infusion during cycle 1, and at least 12 days of BPM31510 infusion during cycle 2. Additionally, patients must have an initial response assessment at the end of cycle 2.

6.6 Other Issues and Further Details

All analyses will be performed using SAS® Version 9.4 or higher. CRAB will follow its SOPs in the creation and quality control of all analysis datasets, tables, figures and listings.

References

SAS Institute Inc. (2010). *SAS/STAT® 9.2 User's guide.* Cary, NC: SAS Institute Inc.

Clopper, C.; Pearson, E. S. (1934). "The use of confidence or fiducial limits illustrated in the case of the binomial." *Biometrical* 26: 404–413.

Kaplan, E.L., and Meier P. (1958). "Nonparametric estimation from incomplete observations." *J Am Stat Assoc, 53:457-481*.

Appendices

Appendix 1: Suggested List of Tables and Figures

Section 1.1 Demographic and Baseline Data

Demographics
Baseline Characteristics
Baseline Laboratory Values

Patient Status
Patient Disposition

Summary of Inclusion/Exclusion
Reasons for Screen Failure

Section 1.2 Efficacy Data
Summary of Primary Efficacy Binary Endpoint
- -Overall Response Rate
- -Response by Visit

Summary of Secondary Efficacy Endpoints
- -OS (table and figure)
- -PFS (table and figure)
- -Response Duration (table and figure)
- -Time to Progression (table and figure)
- -Disease Control Rate
- -CA19-9 Summary

Section 1.3 Safety Data

Overall Summary of Adverse Events
All Adverse Events by System Organ Class and MedDRA Preferred Term
Serious Adverse Events by System Organ Class and MedDRA Preferred Term
Adverse Events that Led to Discontinuation or Delay of Study Drug
Adverse Events Resulting in Death by System Organ Class and MedDRA Preferred Term
Adverse Events by System Organ Class, MedDRA Preferred Term, and Relationship
Adverse Events by System Organ Class, MedDRA Preferred Term, and Maximum Grade
Summary of Prior Medications by WHO ATC Level 2 Text
Summary of Prior Medications by WHO Generic Medication Name
Summary of Concomitant Medications by WHO ATC Level 2 Text
Summary of Concomitant Medications by WHO Generic Medication Name
Summary of Medical History by System Organ Class and MedDRA Preferred Term

Summary of Vitamin K Treatments
Total Exposure to Study Drug
Summary of Deaths
Primary Cause of Death and Relation to Study Drug

Vital Signs and Measurements – Actual and Change from Baseline
ECG Measurements – Actual and Change from Baseline
Hematology – Actual and Change from Baseline
Serum Chemistry – Actual and Change from Baseline
Hematology Change in Grade Shift Table
Serum Chemistry Change in Grade Shift Table
PT, PTT, and INR – Actual and Change from Baseline
PTT and INR Change in Grade Shift Tables
Other – Actual and Change from Baseline (CA 19-9/CEA/CA 125, physical exams, urinalysis, etc.)
Quality of Life – Actual and Change from Baseline Tables for FACT-hep scores
Summary of Adaptive molecular responses as determined by results
Listing of FDG-PET evaluation of tumor response: Change from baseline to 10 weeks by patient

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